REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. Support for the amendment to claim 45 is found in the specification at page 25, lines 33-35, Figure 3 and page 98, under the heading "(8) Activity evaluation."

Claim Rejections Under 35 USC 112, Written Description

For the following reasons, applicants believe that one of skill in the art would reasonably believe that applicants have possession of the claimed invention. Applicants have demonstrated in the specification that the growth of blood vessel tissues by TF is suppressed by the antibody i-b2. Restenosis, angiogenesis and neovascularization all share in common the characteristic that in these disuses the growth of blood vessel tissues is caused by TF.

The in vivo demonstration in the specification of the inhibition of TF to suppress growth of blood vessel tissues is sufficient to demonstrate to one of skill in the art that applicants had possession of the claimed invention. Applicants have shown the suppression of blood vessel tissue growth action by TF after TF expression. Therefore, the inhibitory effect of the antibody i-b2 on the growth of blood vessel tissues, including on angiogenesis and neovascularization by TF, have been shown to be in applicants' possession.

In addition, based on the disclosure of the specification, the site of hTF to which the antibody i-b2 binds has been shown to be a significant site for the blood vessel tissue growth action by TF. This site is also a significant site when a complex comprised of TF and Factor VIIa binds to Factor X (for example, as shown in Reference Example 7 of the present specification). Therefore, it has been demonstrated that antibodies binding to the inhibitory site of the binding of a complex comprised of human TF and Factor VIIa to Factor X can suppress blood vessel tissue growth. As stated in § 2163 of the MPEP, "disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen." *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004). Accordingly, the antibody as claimed in amended claim 45 is described by relevant identifying characteristics that demonstrates the possession of the present invention.

The present claim is defined by the structure of the antibody, and the binding site of the antigen, which is a significant feature in determining the function of an antibody, is specified by "the inhibitory site of the binding of a complex comprised of human TF and Factor VIIa to Factor X upon binding to human TF", so that members that are not related to the invention of the claims in terms of the structure and the function are not included. In addition, the antibody of the present invention can be easily obtained by the method described in Reference Example 7 of the present specification. Furthermore, as mentioned above, there is a relationship between the inhibitory site of the binding to Factor X and the inhibitory effect on the growth of blood vessel tissues. In conclusion, applicants have demonstrated possession of the claimed inveniton.

Claim 55 is further supported because the epitope of the antibody i-b2 is disclosed, so therefore applicants have shown possession of the epitope present on TF and the use of this epitope to obtain an antibody binding to said epitope.

The CDR of the antibody i-b2 of claim 56 is further supported by the disclosure in Tables 1 to 3 of the specification.

Claim Rejections Under 35 USC 112, First Paragraph

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation" MPEP § 2164, quoting from *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 UPSPQ2d 1217, 1223 (Fed. Cir. 1988). "The test of enablement is not whether experimentation is necessary, but whether, if experimentation is necessary, it is undue." MPEP § 2164, quoting from *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Applicants contend, that under the guidelines of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), it would not require undue experimentation to carry out the present invention.

Although the Examiner has agreed that the specification is enabled using the antibody i-b2 to suppress restenosis, there is disagreement with the applicants with respect to whether

other inhibitory effects on other blood vessel tissue growth, such as neovascularization and angiogenesis, are enabled.

As applicants have stated above, although the onset of restenosis, angiogenesis and neovascularization might have different causes, they all share in common TF expression, and the growth of blood vessel tissues caused by TF expression. The antibody of the present invention has been shown to suppress the growth action of blood vessel tissues by TF after TF expression. As the previously submitted Zhang reference shows, the transcription of VEGF/VPF was decreased by transfecting an antisense chain of TF, which demonstates that TF is one of the factors causing angiogenesis and neovascularization. With this in mind, applicants urge that the present claims are enabled for using the present antibody for suppressing the growth of blood vessel tissues, even if the causes of TF expression are different, because Example 3 of the present application clearly shows that the antibody of the present application suppressed the growth of blood vessel tissues.

In response to the Examiner's comments on the HAMA reaction to a non-human derived amino acid sequence, claim 45, the independent claim, now recites that the antibody is "a chimeric antibody or a humanized antibody having a human antibody constant region." These recitations are supported by the specification at page 22, Section 4, entitled "Altered Antibody," as well as by previously presented claim 50.

As suggested by the Examiner, the claims were amended to clarity that TF does not directly bind to Factor X but TF and Factor VIIa to form a complex, and this complex binds to Factor X to activate Factor X by the enzymatic activity of Factor VIIa. This amendment is supported by Reference Example 2(5), Reference Example 7(6) and the like.

Number of working examples

The inhibitory effect of the antibody i-b2 on the growth of blood vessel tissues in restenosis was explicitly confirmed by Example 6, which is sufficient to show enablement of the inhibition of the growth of blood vessel tissues caused by TF expression. Also because it was confirmed that the antibody i-b2 suppressed the growth of blood vessel tissues, it is clear that the site of the binding to TF or the inhibitory site of the binding of a complex comprised of human TF and Factor VIIa to Factor X upon binding to TF is important for the inhibition of growth of blood vessel tissues by TF. Accordingly, applicants contend that the specification of the present application provides sufficient guidance to practice the present invention without undue experimentation.

Scope of the invention, Nature of invention, Level of skill in the art

The specification has shown that the antibody i-b2 suppressed the growth of blood vessel tissues by TF after TF expression, so therefore the growth of blood vessels, caused by disease factors other than restenosis, can be suppressed by the inhibition of TF. Accordingly, a person of skill in the art, with the guidance of the specification, could make and use an antibody according to the present invention without undue experimentation.

Response to arguments

The Examiner pointed out that there was no inhibitory effects of antibody b-b and antibody i-b which binds to TF on restenosis, so the feature of binding to TF cannot be viewed the same as the claimed function. The antibody of the present claims is, however, specified not only by the function of binding to TF but also by "the inhibitory site of the binding of a complex comprised of human TF and Factor VIIa to Factor X upon binding human TF". The antibody binding to such site can be easily made in accordance with Reference Example 7 by one of skill in the art.

The Examiner argues that the inhibitory effect of the antibody b-b and the antibody i-b on restenosis, was not shown in the specification, and therefore binding to TF does not equate with the claimed functionality. Applicants contend that this is a factual misunderstanding. The effects of antibody b-b, antibody i-b and antibody i-b2 on restenosis were disclosed because these antibodies have the same CDR. See Tables 1 to 3. One of skill in the art would understand, however, that antibody b-b, antibody i-b and antibody i-b2 have the same effect. It is clear from Figs. 1 to 4 that these antibodies have almost substantially the same characteristics.

From the description of the document by Zhang et al., it was confirmed in the present invention that even if the roles of TF in tumor and coagulation/restenosis are different, the site of TF to which the antibody i-b2 binds is the site associated with the growth of blood vessel tissues, and the growth of blood vessel tissues is suppressed by binding of the antibody to the site. The site to which the antibody i-b2 binds is the inhibitory site of the binding of a complex comprised of human TF and Factor VIIa to Factor X, which is confirmed in Reference Example 7 of the present application.

Accordingly, applicants believe the present claims are enabled and request withdrawal of the outstanding rejections.

Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Charge Authorization & Petition for Extension

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date January 2, 2008

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